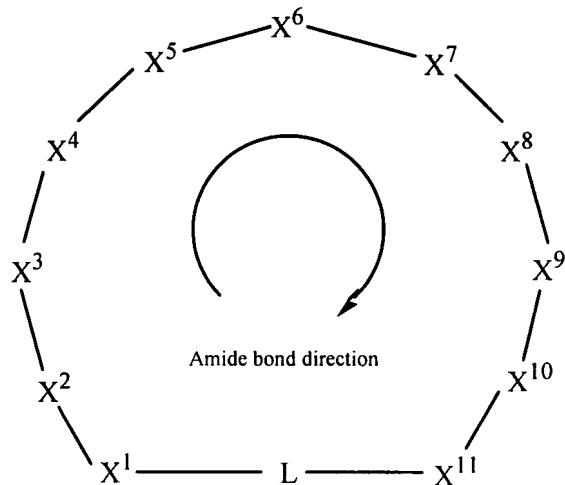


WHAT IS CLAIMED IS:

1. A uPAR-targeting cyclic peptide compound of formula



wherein, each of X¹ through X¹¹ is a D- or L-amino acid, and

X¹ is Val, Cys, HomoCys, Glu, Asp, GluR¹, AspR¹, or Ala;

X² is Ser, Cys, HomoCys, Glu, Asp, GluR¹, AspR¹, or Ala;

X³ is Asn or Gln;

X⁴ is Lys, Arg or His;

X⁵ is Tyr, Trp, Phe, substituted Phe, di-substituted Phe, HomoPhe, β-(3-pyridyl)alanine, β-(2-thienyl)alanine, β-(1-naphthyl)alanine, or β-(2-naphthyl)alanine;

X⁶ is Phe, Tyr, Trp, substituted Phe, di-substituted Phe, HomoPhe, β-(3-pyridyl)alanine, β-(2-thienyl)alanine, β-(1-naphthyl)alanine, or β-(2-naphthyl)alanine;

X⁷ is Ser, Cys, HomoCys, Glu, Asp, GluR¹, AspR¹ or Ala;

X⁸ is Asn, Cys, HomoCys, Glu, Asp, GluR¹, AspR¹ or Ala;

X⁹ is Ile, Leu, Val, NorVal or NorLeu;

X¹⁰ is His, Cys, HomoCys, Glu, Asp, GluR¹, AspR¹ or Ala;

X¹¹ is Trp, Tyr, Phe, substituted Phe, di-substituted Phe, HomoPhe, β-(3-pyridyl)alanine, β-(2-thienyl)alanine, β-(1-naphthyl)alanine, or β-(2-naphthyl)alanine;

wherein R¹ in GluR¹ or AspR¹ is a diamino group -NH-R²-NH₂ bonded to the side chain carbonyl of Glu or Asp, wherein R₂ is an organic residue, said diamino group having the following properties:

- (i) the pK_a of each NH₂ group in a parent diamine H₂N-R²-NH₂ of said R¹ group -NH-R²-NH₂ is less than about 8.0, and
- (ii) the pK_a of the NH₂ group in said R¹ group is less than about 8.0, and

L is a linking unit, such that when X¹ and X¹¹ are linked, the linear dimension between the C ^{α} carbon of amino acid X¹ and the C ^{α} carbon of amino acid X¹¹ is between about 4 and 12 Ångstrom units.

2. The cyclic peptide compound of claim 1, wherein R² is:

- (a) symmetric or non-symmetric with respect to the placement of the amino groups upon it;
- (b) noncyclic or cyclic, which, when cyclic,
 - (i) is heterocyclic, homocyclic, or polycyclic, wherein when it is polycyclic the rings may be fused, unfused or a combination of both fused and unfused, and wherein various of said rings may be homocyclic, heterocyclic or a mixture of both
 - (ii) has the amine groups bonded to the cycle as direct substituents upon the cycle, spaced therefrom or both;
- (c) substituted with one or more substituents,
- (d) -O-(CH₂)_x-O- wherein 10≥x≥2, or
- (e) -CH₂-CO-NH-(CH₂)_x-NH-CO-CH₂- wherein 10≥x≥2.

3. The cyclic peptide compound of claim 1 wherein R² is *p*-phenylene, *o*-phenylene or *m*-phenylene.

4. The compound of claim 1 wherein the linear dimension between the C ^{α} carbon of amino acid X¹ and the C ^{α} carbon of amino acid X¹¹ is between about 5 and 10 Ångstrom units.

5. The compound of claim 4 wherein the linear dimension between the C^α carbon of amino acid X¹ and the C^α carbon of amino acid X¹¹ is between about 6 and 8 Ångstrom units.

6. The compound of claim 1, wherein L is a linker that, reading in the direction X¹-L-X¹¹, is selected from the group consisting of :

- L1 - CO-CH₂-NH-CO-CH₂-CH₂-CH (CO-NH-CH₂-CO-NH₂) -NH- ;
- L2 - CO-CH₂-NH-CO-CH₂-CH₂-CH (CO-NH-CH (CH₂SH) -CO-NH₂) -NH- ;
- L3 - CO-CH (CH₂SH) -NH-CO-CH₂-CH₂-CH (CO-NH-CH₂-CONH₂) -NH- ;
- L4 - CO-CH₂-NH-CO-CH₂-CH₂-CH (CO-NH-CH (CH₂CH₂SH) -CO-NH₂) -NH- ;
- L5 - CO-CH (CH₂CH₂SH) -NH-CO-CH₂-CH₂-CH (CO-NH-CH₂-CONH₂) -NH- ;
- L6 - CO-CH (CH₂CH₂COR¹) -NH-CO-CH₂-CH₂-CH (CO-NH-CH₂-CONH₂) -NH- ;
- L7 - CO-CH (CH₂COR¹) -NH-CO-CH₂-CH₂-CH (CO-NH-CH₂-CONH₂) -NH- ;
- L8 - CO-CH₂-NH-CO-CH₂-CH₂-CH (CO-NH-CH (CH₂CH₂COR¹) -CO-NH₂) -NH- ;
- L9 - CO-CH₂-NH-CO-CH₂-CH₂-CH (CO-NH-CH (CH₂COR¹) -CO-NH₂) -NH- ;
- L10 - CO-CH₂-NH-CO-CH₂-CH₂-CH (CO-NH-CH₂-COR¹) -NH- ;
- L11 - CO-CH (CH₂CH₂COOH) -NH-CO-CH₂-CH₂-CH (CO-NH-CH₂-CONH₂) -NH- ;
- L12 - CO-CH (CH₂COOH) -NH-CO-CH₂-CH₂-CH (CO-NH-CH₂-CONH₂) -NH- ;
- L13 - CO-CH₂-NH-CO-CH₂-CH₂-CH (CO-NH-CH (CH₂CH₂COOH) -CO-NH₂) -NH- ;
- L14 - CO-CH₂-NH-CO-CH₂-CH₂-CH (CO-NH-CH (CH₂COOH) -CO-NH₂) -NH- ; and
- L15 - CO-CH₂-NH-CO-CH₂-CH₂-CH (CO-NH-CH₂-CO-NH-R¹) -NH- ,

wherein R¹ in any of L6-L10 is a diamino group -NH-R²-NH₂ wherein R² is an organic residue, said diamino group having the following properties:

- (i) the pK_a of each NH₂ group in a parent diamine H₂N-R²-NH₂ of said R¹ group -NH-R²-NH₂ is less than about 8.0; and
 - (ii) the pK_a of the NH₂ group in said -NH-R²-NH₂ is less than about 8.0.
- and wherein R¹ in L15 is an organic residue.

7. The compound of claim 2, wherein L is a linker that, reading in the direction X¹-L-X¹¹, is selected from the group consisting of :

- L1 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CO-NH₂)-NH- ;
 L2 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH(CH₂SH)-CO-NH₂)-NH- ;
 L3 -CO-CH(CH₂SH)-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CONH₂)-NH- ;
 L4 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH(CH₂CH₂SH)-CO-NH₂)-NH- ;
 L5 -CO-CH(CH₂CH₂SH)-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CONH₂)-NH- ;
 L6 -CO-CH(CH₂CH₂COR¹)-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CONH₂)-NH- ;
 L7 -CO-CH(CH₂COR¹)-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CONH₂)-NH- ;
 L8 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH(CH₂CH₂COR¹)-CO-NH₂)-NH- ;
 L9 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH(CH₂COR¹)-CO-NH₂)-NH- ;
 L10 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-COR¹)-NH- ;
 L11 -CO-CH(CH₂CH₂COOH)-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CONH₂)-NH- ;
 L12 -CO-CH(CH₂COOH)-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CONH₂)-NH- ;
 L13 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH(CH₂CH₂COOH)-CO-NH₂)-NH- ;
 L14 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH(CH₂COOH)-CO-NH₂)-NH- ; and
 L15 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CO-NH-R¹)-NH- ,

wherein R¹ in any of L6-L10 is a diamino group -NH-R²-NH₂ wherein R² is an organic residue, said diamino group having the following properties:

- (i) the pK_a of each NH₂ group in a parent diamine H₂N-R²-NH₂ of said R¹ group -NH-R²-NH₂ is less than about 8.0; and
- (ii) the pK_a of the NH₂ group in said -NH-R²-NH₂ is less than about 8.0.

and wherein R¹ in L15 is an organic residue.

8. The compound of claim 3, wherein L is a linker that, reading in the direction X¹-L-X¹¹, is selected from the group consisting of :

- L1 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CO-NH₂)-NH- ;
 L2 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH(CH₂SH)-CO-NH₂)-NH- ;
 L3 -CO-CH(CH₂SH)-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CONH₂)-NH- ;
 L4 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH(CH₂CH₂SH)-CO-NH₂)-NH- ;
 L5 -CO-CH(CH₂CH₂SH)-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CONH₂)-NH- ;
 L6 -CO-CH(CH₂CH₂COR¹)-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CONH₂)-NH- ;

- L7 -CO-CH(CH₂COR¹)-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CONH₂)-NH- ;
- L8 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH(CH₂CH₂COR¹)-CO-NH₂)-NH- ;
- L9 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH(CH₂COR¹)-CO-NH₂)-NH- ;
- L10 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-COR¹)-NH- ;
- L11 -CO-CH(CH₂CH₂COOH)-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CONH₂)-NH- ;
- L12 -CO-CH(CH₂COOH)-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CONH₂)-NH- ;
- L13 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH(CH₂CH₂COOH)-CO-NH₂)-NH- ;
- L14 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH(CH₂COOH)-CO-NH₂)-NH-; and
- L15 -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CO-NH-R¹)-NH- ,

wherein R¹ in any of L6-L10 is a diamino group -NH-R²-NH₂ wherein R² is an organic residue, said diamino group having the following properties:

- (i) the pK_a of each NH₂ group in a parent diamine H₂N-R²-NH₂ of said R¹ group -NH-R²-NH₂ is less than about 8.0; and
- (ii) the pK_a of the NH₂ group in said -NH-R²-NH₂ is less than about 8.0.

and wherein R¹ in L15 is an organic residue.

9. The cyclic peptide compound of claim 6, 7 or 8, wherein R² in any of L6-L10 is:
 - (a) symmetric or non-symmetric with respect to the placement of the amino groups upon it;
 - (b) noncyclic or cyclic, which, when cyclic,
 - (i) is heterocyclic, homocyclic, or polycyclic, wherein
 - when it is polycyclic the rings may be fused, unfused or a combination of both fused and unfused, and wherein various of said rings may be homocyclic, heterocyclic or a mixture of both
 - (ii) has the amine groups bonded to the cycle as direct substituents upon the cycle, spaced therefrom or both;
 - (c) substituted with one or more substituents;
 - (d) -O-(CH₂)_x-O- wherein 10≥x ≥2; or
 - (e) -CH₂-CO-NH-(CH₂)_x-NH-CO-CH₂- wherein 10≥x ≥2.

10. The compound of claim 6, 7 or 8 wherein R² in any of L6-L10 is *p*-phenylene, *o*-phenylene or *m*-phenylene.

11. The compound of claim 1, 2, 3, 6, 7 or 8, wherein, when X¹ - X¹¹ is SEQ ID NO:2, L is not -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CO-NH₂)-NH-

12. The compound of claim 6, wherein X¹ - X¹¹ is SEQ ID NO:2, L is -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-COR¹)-NH- and R¹ is -NH-*p*-phenylene-NH₂.

13. The compound of claim 6, 7 or 8 wherein L is -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CO-NH-R¹)-NH-

14. The compound of claim 6, 7 or 8 wherein the L chain is -CO-CH₂-NH-CO-CH₂-CH₂-CH(CO-NH-CH₂-CO-NH-R¹)-NH- and R¹ in said L chain is phenyl.

15. The compound of claim 14 wherein X¹ - X¹¹ is SEQ ID NO:2

16. The compound of claim 1, 2, 3, 6, 7 or 8, wherein any one of X⁵, X⁶ or X¹¹ is substituted or disubstituted Phe.

17. The compound of claim 16 wherein said phenylalanine is substituted or disubstituted with a substituent selected from the group consisting of

- (a) a halo;
- (b) a nitro;
- (c) a C1-C6 straight or branched chain alkyl; and
- (d) in the case of disubstituted Phe, any two of (a)-(c).

18. The compound of claim 1, 2 or 3 wherein, when said linker L includes a Cys, HomoCys, Glu, Asp, GluR¹ or AspR¹ amino acid residue, said amino acid residue is a D- or L-enantiomer.

19. The compound of claim 1, 2, 3, 6, 7 or 8, having an IC₅₀ value in a competitive binding assay to uPA receptor *in vitro* of less than about 10⁻⁵ molar

20. The compound of claim 19 having an IC₅₀ value in a competitive binding assay to uPA receptor *in vitro* of less than about 10⁻⁶ molar.

21. The compound of claim 20 having an IC₅₀ value less than about 10⁻⁷ molar.

22. A uPAR-targeting pharmaceutical composition comprising:

- (a) the cyclic peptide compound of any of claims 1, 2, 3, 6, 7 and 8; and
- (b) a pharmaceutically acceptable carrier.

23. The pharmaceutical composition of claim 22 in a form suitable for injection.

24. A uPAR-targeting therapeutic composition comprising :

- (a) an effective amount of the compound of any of claims 1, 2, 3, 6, 7, 8 bound directly or indirectly a therapeutically active moiety; and
- (b) a therapeutically acceptable carrier.

25. The composition of claim 24 in a form suitable for injection.

26. The composition of claim 24, wherein said moiety is a radionuclide.

27. The composition of claim 26, wherein said radionuclide is selected from the group consisting of ¹²⁵I, ¹³¹I, ⁹⁰Y, ⁶⁷Cu, ²¹⁷Bi, ²¹¹At, ²¹²Pb, ⁴⁷Sc, and ¹⁰⁹Pd.

28. A method for inhibiting cell migration, cell invasion, cell proliferation or angiogenesis, or for inducing apoptosis, comprising contacting cells associated with undesired cell migration, invasion, proliferation or angiogenesis with an effective amount of the compound of any of claims 1, 2, 3, 6, 7 or 8.

29. A method for inhibiting cell migration, cell invasion, cell proliferation or angiogenesis, or for inducing apoptosis, comprising contacting cells associated with undesired cell migration, invasion, proliferation or angiogenesis with an effective amount of the composition of claim 22.

30. A method for inhibiting cell migration, cell invasion, cell proliferation or angiogenesis, or for inducing apoptosis, comprising contacting cells associated with undesired cell migration, invasion, proliferation or angiogenesis with an effective amount of the composition of claim 24.

31. A method for inhibiting the invasiveness of tumor cells comprising contacting said cells with an effective amount of the compound of any of claims 1, 2, 3, 6, 7 or 8.

32. A method for inhibiting the invasiveness of tumor cells comprising contacting said cells with an effective amount of the composition of claim 22.

33. A method for inhibiting the invasiveness of tumor cells comprising contacting said cells with an effective amount of the composition of claim 24.

34. A method for treating a subject having a disease or condition associated with undesired cell migration, invasion, proliferation, or angiogenesis, comprising administering to said subject an effective amount of a pharmaceutical composition according to claim 22.

35. A method for treating a subject having a disease or condition associated with undesired cell migration, invasion, proliferation, or angiogenesis, comprising administering to said subject an effective amount of a pharmaceutical composition according to claim 23.

36. A method for treating a subject having a disease or condition associated with undesired cell migration, invasion, proliferation, or angiogenesis, comprising administering to said subject an effective amount of a pharmaceutical composition according to claim 24.

37. A method for treating a subject having a disease or condition associated with undesired cell migration, invasion, proliferation, or angiogenesis, comprising administering to said subject an effective amount of a pharmaceutical composition according to claim 25.

38. A method for treating a subject having a disease or condition associated with undesired cell migration, invasion, proliferation, or angiogenesis, comprising administering to said subject an effective amount of a pharmaceutical composition according to claim 26.

39. A method for treating a subject having a disease or condition associated with undesired cell migration, invasion, proliferation, or angiogenesis, comprising administering to said subject an effective amount of a pharmaceutical composition according to claim 27.

40. A method according to-claim 34-39, wherein said disease or condition is primary growth of a solid tumor, leukemia or lymphoma; tumor invasion, metastasis or growth of tumor metastases; benign hyperplasia; atherosclerosis; myocardial angiogenesis; post-balloon angioplasty vascular restenosis; neointima formation following vascular trauma; vascular graft restenosis; coronary collateral formation; deep venous thrombosis; ischemic limb angiogenesis; telangiectasia; pyogenic granuloma; corneal disease; rubeosis; neovascular glaucoma; diabetic and other retinopathy; retrobulbar fibroplasia; diabetic neovascularization; macular degeneration; endometriosis; arthritis; fibrosis associated with a chronic inflammatory condition, traumatic spinal cord injury including ischemia, scarring or fibrosis; lung fibrosis, chemotherapy-induced fibrosis; wound healing with scarring and fibrosis; peptic ulcers; a bone fracture; keloids; or a disorder of vasculogenesis, hematopoiesis, ovulation, menstruation, pregnancy or placentation associated with pathogenic cell invasion or with angiogenesis.

41. A method according to claim 40, wherein said disease is tumor growth, invasion or metastasis.

42. A diagnostically useful uPAR-targeting ligand composition comprising:
- (a) the compound of any of claims 1, 2, 3, 6, 7, 8 which is diagnostically labeled;
 - (b) a diagnostically acceptable carrier.

43. The composition of claim 42 wherein the detectable label is a radionuclide, a PET-imageable agent, a fluorescer, a fluorogen, a chromophore, a chromogen, a phosphorescer, a chemiluminescer or a bioluminescer.

44. The composition of claim 43 wherein said radionuclide is selected from the group consisting of ^3H , ^{14}C , ^{35}S , ^{99}Tc , ^{123}I , ^{125}I , ^{131}I , ^{111}In , ^{97}Ru , ^{67}Ga , ^{68}Ga , ^{72}As , ^{89}Zr and ^{201}Tl .

45. The composition of claim 43, wherein said fluorescer or fluorogen is fluorescein, rhodamine, dansyl, phycoerythrin, phycocyanin, allophycocyanin, *o*-phthal-dehyde, fluorescamine, a fluorescein derivative, Oregon Green, Rhodamine Green, Rhodol Green or Texas Red.

46. A method for detecting the presence of uPAR (i) on the surface of a cell, (ii) in a tissue, (iii) in an organ or (iv) in a biological sample, which cell, tissue, organ or sample is suspected of expressing uPAR due to a pathological state, comprising :

- (a) contacting said cell, tissue, organ or sample with the diagnostic composition of claim 42; and
- (b) detecting the presence of said label associated with said cell, tissue, organ or sample.

47. A method according to claim 46, wherein said contacting is *in vivo*.

48. A method according to claim 46, wherein said contacting and said detecting are *in vivo*.

49. An affinity ligand useful for binding to or isolating uPAR, comprising the compound of any of claims 1, 2.,-3, 6, 7, 8 immobilized to a solid support or carrier.

50. A method for isolating uPAR from a complex mixture comprising:
- (a) contacting said mixture with the affinity ligand of claim 49;
 - (b) allowing any uPAR to bind to said ligand;

- (c) removing unbound material from said ligand; and
- (d) eluting said bound uPAR,
thereby isolating said uPAR.

51. A method for isolating or enriching uPAR-expressing cells from a cell mixture, comprising

- (a) contacting said cell mixture with the uPAR-binding ligand compound of any of claims 1, 2, 3, 6, 7, 8;
- (b) allowing any uPAR-expressing cell to bind to said compound;
- (c) separating cells bound to said ligand from unbound cells; and
- (d) removing said bound cells from said ligand,

thereby isolating or enriching said uPAR-expressing cells.

52. A method for isolating or enriching uPAR-expressing cells from a cell mixture, comprising

- (a) contacting said cell mixture with the affinity ligand of claim 49;
- (b) allowing any uPAR-expressing cell to bind to said ligand;
- (c) removing unbound cells from said ligand and from said bound cells; and
- (d) releasing said bound cells,

thereby isolating or enriching said uPAR-expressing cells.